Shape Optimizing Diffeomorphisms for Computational Biology

Symmetric, Dataset Specific Analysis of Neurodegeneration and Correlated Variables

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SPECIFIC AIMS

One of the most challenging problems in modern neuroimaging is detailed characterization of neurodegeneration. Quantifying spatial and longitudinal atrophy patterns is fundamental to this process. These spatiotemporal signals will aid in diagnostics and discriminating between related diseases, such as corticobasal degeneration (CBD), frontotemporal dementia (FTD) and Alzheimer's disease (AD), which manifest themselves in the same at-risk population with complex effects on behavior.

Aim 1: This proposal will contribute a new UPenn-UCLA collaboration for implementing rigorous symmetric and specific volumetric spatiotemporal medical image analysis in a large scale computing environment.

Aim 2: We disseminate an ITK-based diffeomorphic image analysis system that will dramatically enhance the neuroimaging community's quantitative understanding of normal and pathological (FTD, AD, and CBD) aging and correlated (genetic, behavioral) variables.

Aim 3: We evaluate and refine the developed methodology. Second, we perform studies of structure-function association under neurodegeneration using both our new tools and CCB surface-based analysis.

BACKGROUND & SIGNIFICANCE

Symmetric Diffeomorphisms: A diffeomorphism [1] is a differentiable map with a differentiable inverse. Symmetric diffeomorphisms (DM) exist in the discrete world of image domains and are guaranteed to be optimal paths from image *I* to *J* and from *J* to *I*. See figure 1 and references [2-3].
Specific Diffeomorphic Templates: A template summarizes information from an interesting dataset. A specific (figure 2) diffeomorphic template evolves in space and time to represent the average shape and appearance of a population.
Significant Collaboration: This effort brings together two major neuroimaging research institutions to share and disseminate data and algorithms via the NCBC collaboration program. The UPenn team of mathematicians, neurologists and computational/ITK experts will participate in common goals with the UCLA CCB groups and core members.
Significant Evaluation: Both teams will be engaged in evaluating and comparing the novel UPenn contributions to the existing CCB data processing environment.
Significant Computation: The large-scale computing needs for DM will leverage the computational resources of the UCLA CCB in application to large scale automated clinical studies and atlas generation.
Clinical Significance: This project blends neuroscience and engineering to address pressing challenges in medicine. The resulting mapping techniques will chart the impact of dementia on the human brain and map how treatment combats disease.

PRELIMINARY STUDIES

Evaluating Symmetric Diffeomorphisms: We recently showed solving the following equation, which uses symmetric diffeomorphisms and generates an optimal template:

$$E(I,\{J^i\}) = \sum_i \int_{t=0}^{0.5} \left(\|\mathbf{v}_1^i\|_L^2 + \|\mathbf{v}_2^i\|_L^2 \right) dt + \|I(\phi_1^i(\mathbf{x},0.5)) - J_i(\phi_2^i(\mathbf{x},0.5))\|^2$$

outperforms small deformation methods + biased templates.

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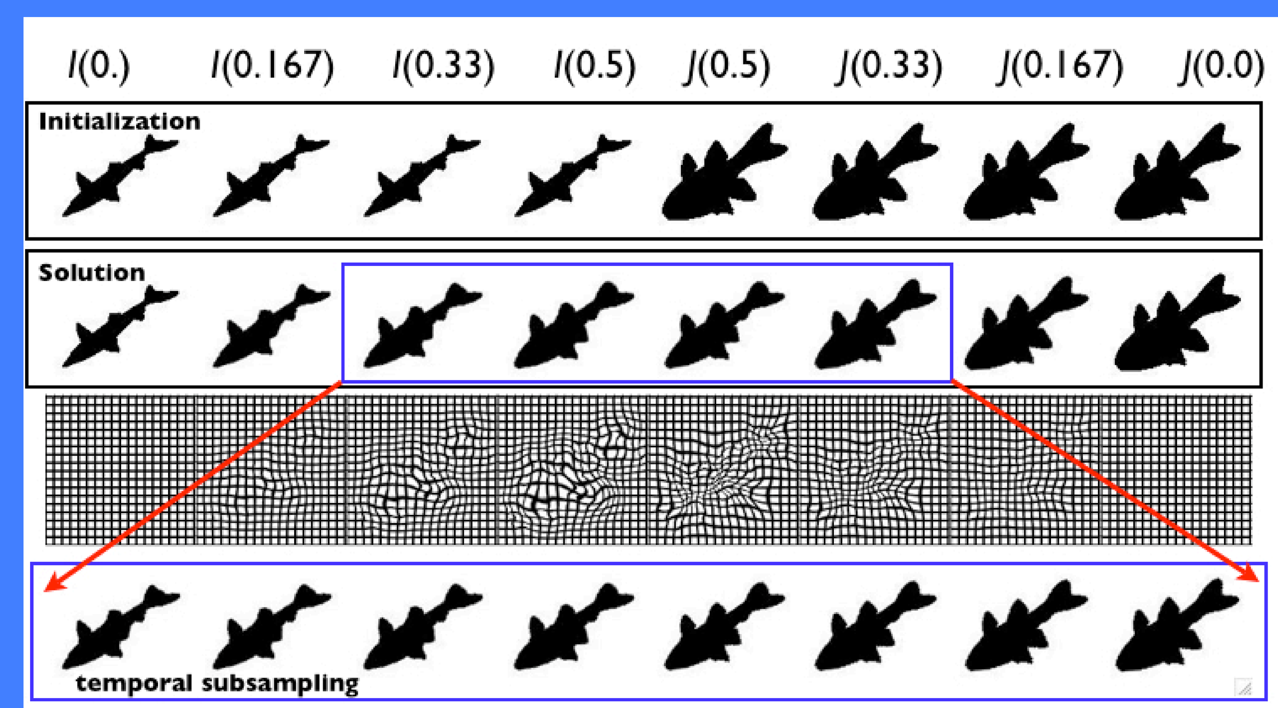


Fig. 1. Illustration of symmetric normalization of an image pair.

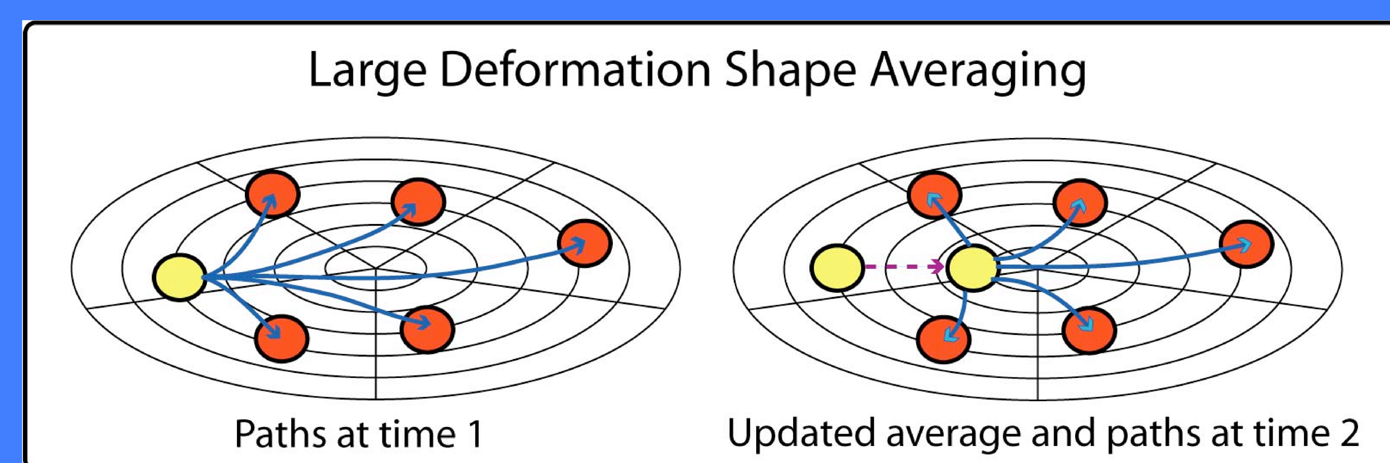


Fig. 2. Illustration of symmetric template generation.

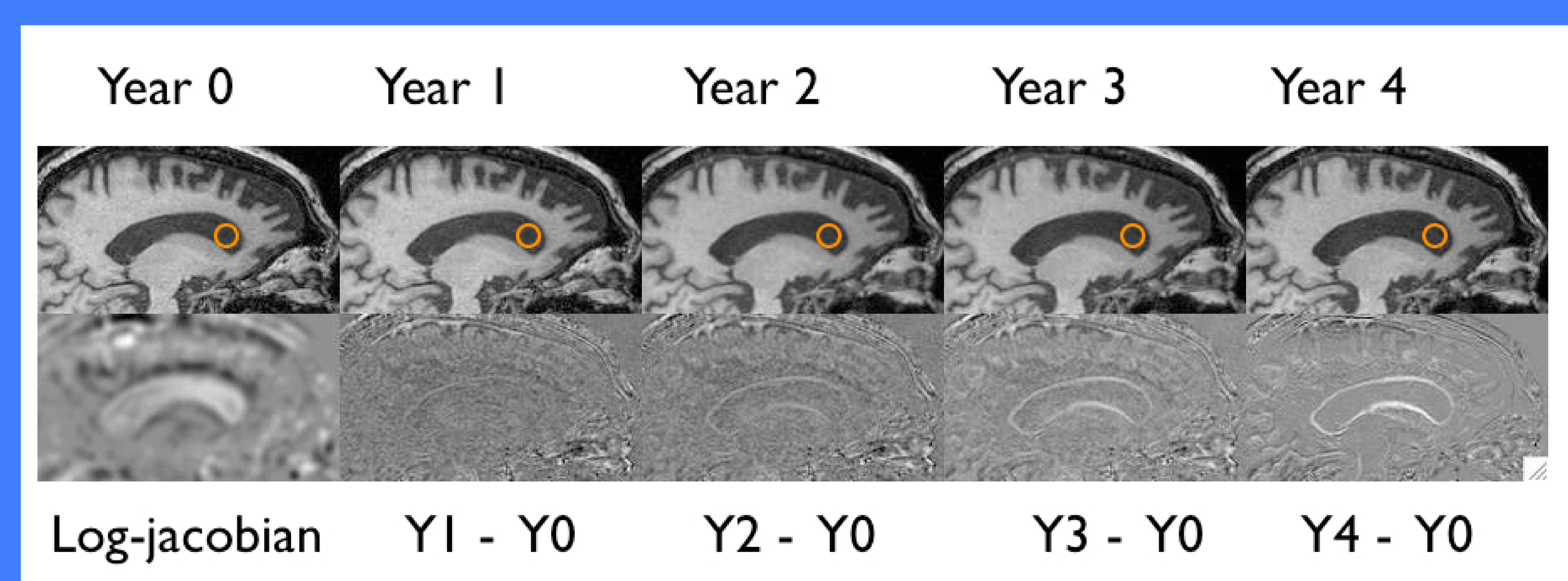


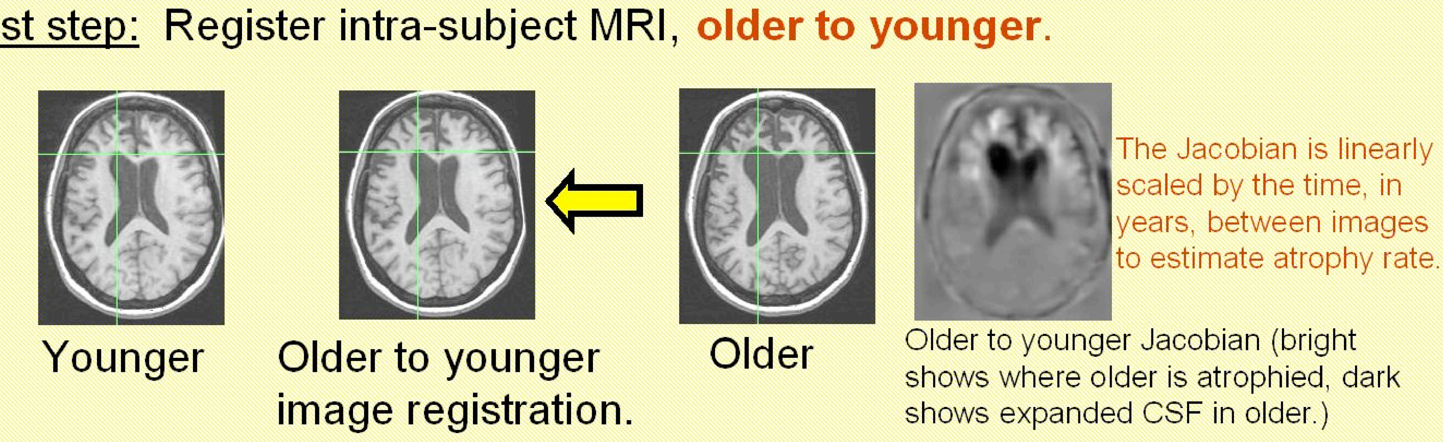
Fig. 3. We estimate atrophy at year 1 from year 0 and year 4 using a symmetric diffeomorphic mapping in space and time.

Map longitudinal FTD change to common space

Input longitudinal patient data and FTD atlas.

The atlas has gray matter and structural segmentations.

First step: Register intra-subject MRI, older to younger.



Second Step: Skull strip and register younger MRI to atlas MRI.

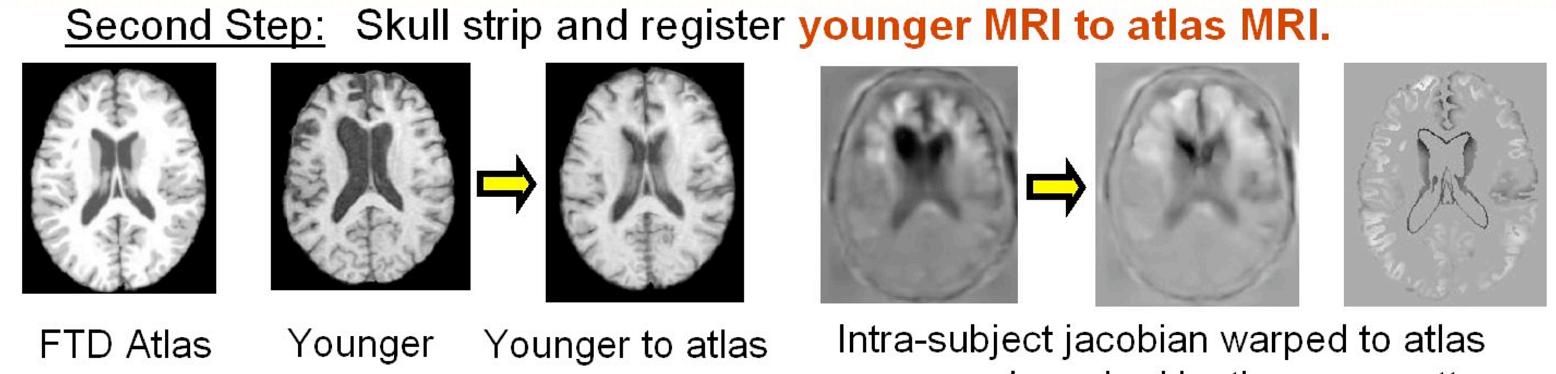


Fig. 4. A diagnosed FTD individual from our population is normalized with our large deformation methods to capture both the temporal atrophy and to normalize to common space.

PRELIMINARY STUDIES

Symmetric Diffeomorphisms for Longitudinal Analysis: We recently applied the methods of Fig. 3 and 4. to study FTD effects [4]. Average annual expansion and atrophy from FTD is in the average FTD atlas space in Fig. 5. Our methods enabled us to quantify annual atrophy and subsequently relate annual atrophy to decline in neurocognitive scores.

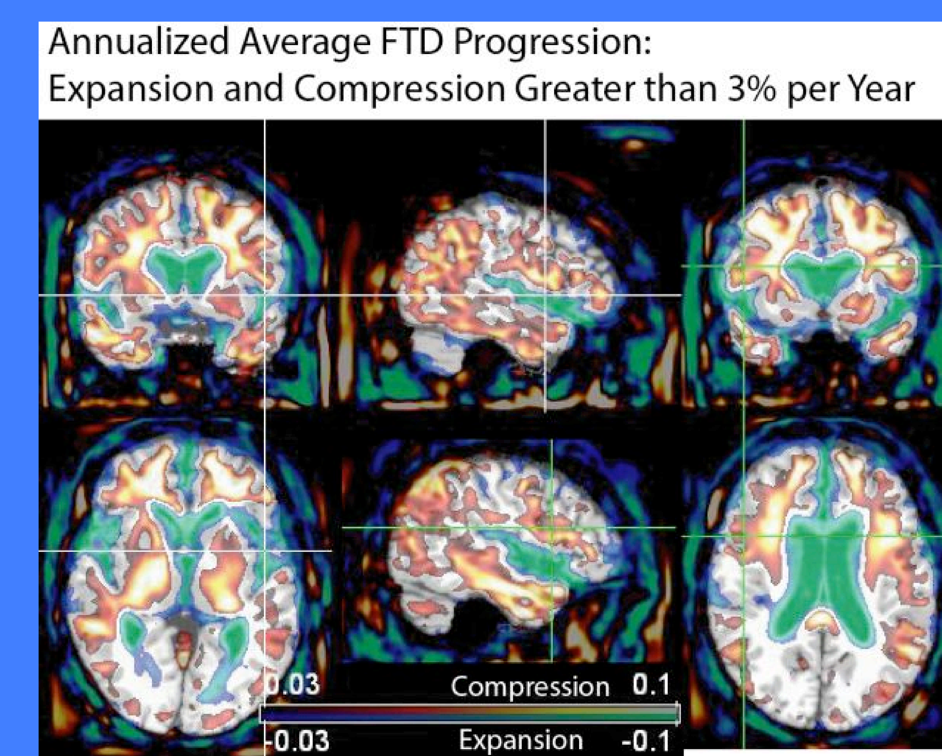


Fig. 5. We use the approach shown in Fig. 3 and Fig. 4 to generate a population map of the atrophy pattern caused by severe FTD over a known period of time.

RESEARCH DESIGN AND METHODS

Summary Aim 1: Our proposal will introduce a new motivating problem and dataset to the CCB: quantifying the complex relationship between grammar/sentence comprehension and neurodegeneration. Common implementation platforms will use ITK and allow for clustering and parallelism to be shared.
Summary Aim 2: Aim 2 methodology will test computational biology strategies across spatial scales and biological systems. Our population analysis numerical methods will improve the applicability of neuroimaging quantification to general real-world problems and large datasets. The ITK-CCB public distribution of the methods will ensure the benefit of researchers at large.
Summary Sub-Aim 3a: We will characterize, in detail, some important aspects of structure-function associations under normal and neurodegenerative conditions. The results will be important clinically as accurately diagnosed patients with AD, FTD or CBD can then be recruited for clinical trials directed at the specific disease mechanisms underlying each condition. Families can then be provided with accurate prognostic information for long-term planning.
Summary Sub-Aim 3b: The new CCB image analysis tools augmented by the availability of our optimal brain templates will map early changes in those at heightened genetic risk for AD, and yield biomarkers for disease progression.This will contribute to the first CCB DBP by storing dynamic maps of brain degeneration and creating a framework to compare dynamic maps within and across populations.

RELEVANT PAPERS

1. M. Miller, et. al. "On the metrics and Euler-Lagrange equations of computational anatomy," *Annu. Rev. Biomed. Eng*, 2002.
2. B. Avants, et. al., "Landmark and intensity-driven lagrangian frame diffeomorphic image registration: Application to structurally and functionally based inter-species comparison," *MIA*, 2005.
3. Avants B., Gee J.C.. Geodesic estimation for large deformation deformation anatomical shape and intensity averaging *Neuroimage*. 2004;Suppl 1:S139-150.
4. Avants B, Grossman M, Gee JC, The Correlation of Cognitive Decline with Frontotemporal Dementia Induced Annualized Gray Matter Loss using Diffeomorphic Morphometry, *ADAD, 2005.*